REMARKS/ARGUMENTS

Reconsideration of this application and entry of the foregoing amendments are respectfully requested.

Claims 20 and 21 have been revised to include the limitation of now cancelled claim 28. Claims 22 and 24 have also been cancelled and claims 25-27 have been revised to conform with the language of the claims from which they depend. New claims 29 and 30 have been added. These new claims are not believed to be subject to the current rejection under 35 USC 112, first paragraph, as the genus is not "indeterminate". That the claims have been revised should not be taken as an indication that Applicant agrees with any position taken by the Examiner. Rather, the revisions are offered merely to advance prosecution and Applicant reserve the right to pursue deleted subject matter in a continuation application.

Claims 20-22 and 24-27 stand rejected under 35 USC 112, first paragraph, as allegedly lacking written description. Withdrawal of the rejection is submitted to be in order in view of the revision of the claims to include the limitation of claim 28 which was not subject to the rejection.

Reconsideration is requested.

Claims 20-22, 24, 25 and 28 stand rejected under 35 USC 102(e) as allegedly being anticipated by Mitrani. Withdrawal of the rejection is submitted to be in order for the reasons that follow.

As pointed out previously, it was a new and non-obvious finding on the part of Applicant that Activin can be used to promote healing with reduced scarring. The effects of Activin on scarring are dose dependent. That is, different doses have markedly different effects on scarring. The doses described in the present specification all have beneficial effects on scarring (when assessed either macroscopically or microscopically). As previously discussed by Applicant, the

doses considered by Mitrani are far higher than those shown by Applicant to promote healing with reduced scarring. The doses suggested by Mitrani would actually increase scarring.

The Examiner is reminded that Mitrani suggests that activin should be used in a dose range of between 0.001mg/kg and 50mg/kg body weight; preferred dose ranges of activin are stated to be between 0.01mg/kg and 10mg/kg body weight.

The studies described in the instant application utilized rats weighing between 200g and 250g. These were treated with one of three separate regimes:

i) three administrations, each of 2.5ng;

ii) three administrations, each of 5ng; or

iii) three administrations, each of 10ng.

Thus, in the lowest dosing regime, a total of 7.5ng of activin was administered per rat, and in the highest dosing regime, a total of 30ng of activin was administered per rat. These totals, respectively, correspond to between 34.1 and 30ng/kg body weight (depending on size of rat) and between 136.4 and 120ng/kg body weight.

Applicant again emphasizes that these doses are considerably lower than those suggested in Mitrani. The lowest dose considered by Mitrani corresponds to 1μg/kg, and the lowest preferred dose to 10μg/kg. In contrast, the highest dose shown by Applicant to reduce scarring is 0.136μg/kg (about one eighth of the lowest suggested by Mitrani), and the lowest dose is only 0.03μg/kg (just 3% of the lowest dose suggested by Mitrani). The skilled person following the teachings of Mitrani would not have arrived at a scar-reducing dose of Activin, as required by the instant invention.

As Applicant noted previously, doses in the range of those suggested by Mitrani have been shown to be pro-scarring, rather than anti-scarring. By way of example, transgenic mice

that over-express Activin A in the basal epidermis (calculated to lead to between 20 and 150ng activin/ml blood – Munz et al 1999) exhibit enhanced scarring in response to full thickness excisional wounds (unpublished data from Munz et al, and described in Wankell et al 2003, and Sulyok et al 2004 – copies attached).

The Examiner's attention is respectfully directed to the disclosure at page 128 of Sulyok et al, particularly, that under heading 2. This reports on the results of wound healing studies undertaken in transgenic mice over-expressing Activin (under the control of a keratin promoter). In particular, the final paragraph under heading 2 notes:

> "After skin injury, a striking enhancement of the healing process was observed. In particular, the area of granulation tissue was more extended, and an increase in reepithelialisation was also seen in most of the animals (Munz et al., 1999b). Unfortunately, however, the accelerated healing process **resulted in enhanced scarring** ... Thus, enhancing the levels of activin in the wound increased the speed of healing, but impaired the quality of repair." (Emphasis added.)

Applicant submits that this passage, when taken in combination with the results set out in the specification of the instant application, clearly illustrates that the effect of Activin on scarring is dose-dependent, being anti-scarring at low dose and pro-scarring at high dose (it should be noted that, in this context, **all** doses considered in the present application should be considered to be "low doses", as compared to the "high doses" suggested in the prior art and achieved in the cited papers).

The Examiner is reminded that rats of 200 to 250g weight have an average blood volume of approximately 13.5mls. Thus, rats treated with regime (iii) above can be expected to achieve a total accumulation of 2.22ng Activin/ml blood (based on administration of a total of Activin 30ng activin, and assuming no breakdown of activin). This figure (for the highest dose regime contemplated by Applicant) is approximately one tenth of the lowest value reported by Munz et

al in mice exhibiting increased scarring. In turn, the lowest concentration of Activin reported by Munz et al (approximately ten times that established by regime (iii)) is generally comparable with that arising from the lowest dose considered by Mitrani (approximately eight times that established by regime (iii)).

It will be clear from above and attached publications that an artisan, following the teachings of Mitrani, would not have arrived at the subject matter of the present claims (e.g., use of Activin in an amount sufficient to reduce scarring) but would, in fact, have been led to use amounts of Activin that would increase scarring. Accordingly, reconsideration is requested.

Claims 20-22, 24, 25 and 28stand rejected under 35 USC 102(b) as allegedly being anticipated by De Kretser. Withdrawal of the rejection is submitted to be in order for the reasons that follow.

The disclosure of De Kretser et al is entirely silent as to doses of activin that are to be used. Given the lack of this teaching, the dose dependency discussed above and the evidence submitted herewith, De Kretser et al cannot be viewed as being inherently anticipatory. Accordingly, reconsideration is requested.

Claims 20, 21, 26 and 27 stand rejected under 35 USC 103 as allegedly being obvious over Mitrani in view of Ferguson. These same claims stand rejected as obvious over De Kretser et al in view of Ferguson. The rejections are traversed for the reasons that follow.

The fundamental failings of Mitrani and De Kretser are detailed above. Nothing in Ferguson would have cured the deficiencies of the primary references. Reconsideration is, therefore, requested.

As regards the Information disclosure Statement filed November 9, 2006, the Examiner's attention is directed to the fact that JP-A-6-506360 corresponds to WO 92/15323 (which is in

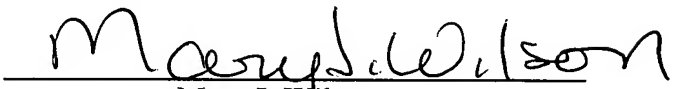
English) and JP-A-10-509592 corresponds to WO 96/15226 (which is also in English). Accordingly, the Examiner is requested to initial and return the attached further copy of the PTO/SB/08a Form submitted November 9, 2006 (on which all four of these documents are listed).

The Examiner is also requested to consider the documents and to initial and return the PTO/SB/08a Form listing same that is submitted herewith.

This application is submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: 

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